Study Background Information

Study Title: Case-Control Study of Testicular Germ Cell Cancer Among U.S. Military Servicemen. This study is also known as ***S**ervicemen's **T**esticular tumor **E**nvironmental **E**ndocrine **D**eterminants (**STEED**) Study.*

This study is a collaborative project between the National Cancer Institute (NCI) and the U.S. Department of Defense (DOD). The overall objective is to conduct an etiologic study of testicular cancer among U.S. servicemen to better understand the epidemiology of a multi-factorial cancer.

Testicular germ cell cancer is one of the most common cancers in young men between the ages of 15 and 35 years. Most testicular tumors (95%) originate in the germ cells, the special sperm-forming cells within the testicles. The American Cancer Society estimates that about 7,000 new cases of testicular cancer are diagnosed each year in the United States. According to 1995-97 SEER data, the lifetime risk of being diagnosed with any form of testicular cancer is only 0.35% and the lifetime risk of dying from it is 0.02% for all males. This rate is higher for white males (0.40% and 0.02%) than for black males (0.08% and 0.02%). Although a rare cancer, testicular cancer has captured the interest of NCI due to the pronounced rise in incidence rates in the United States and other industrialized countries during the past several decades. The annual incidence of testicular cancer in all U.S. men has increased from 3.2/100,000 in 1976 to 4.8/100,000 in 1997, an increase of 1.8%. However, the increase during this period was 2.9% among whites and only 0.8% among blacks. It was also higher among younger age groups under the age of 50 where the increase among white males was 3.6%.

NCI has chosen United States servicemen as an ideal candidate study population in which to evaluate the etiology of testicular cancer because (1) incidence rates are higher than that of the general population, (2) there is a large concentration of men in higher risk age groups, (3) DoD maintains subject's blood sample, historical, personal, occupational, and medical records useful to the study, and (4) the study can rely on the Department of Defense Tumor Registry as a source of cases.

A. Potential Genetic and Environmental Risk Factors

The observed increase in testicular cancer is likely to be attributable to genetic and environmental factors although the relationship between them and the relative importance of either factor remains a research concern. Incidence patterns suggest that genetic, congenital, and hormonal factors are involved. It is well established that white males, those with a first degree relative affected, and those with a history of cryptorchidism, a condition in which boys are born with undescended testicles, are at higher risk to testicular cancer.

Genetic. In addition to young, white males, elevated risk of testicular cancer is found among men with a family history of testicular cancer. Elevated risk has been found in twins of affected men, and in father-son pairs (Swerdlow et al, 1997; Han & Peschel, 2000; Nicholson & Harland, 1995). Researchers also have discovered a region on the X chromosome (Xq27) that is shared between related individuals who have testicular cancer far more often than is expected by chance. It is inherited by the patient's mother, who in turn inherited it from either her mother or father. It is hoped that isolation of a gene for testicular cancer may soon follow and help shed light on the role of genetic susceptibility (Rapley et al, 2000).

Congenital abnormalities. A history of cryptorchidism (a condition in which boys are born with undescended testicles) is a well-established risk factor for testicular cancer. Up to 10 percent of testicular tumors are diagnosed in males with a history of an undescended testicle. A male with a history of cryptorchidism has a risk of developing testicular cancer that is 2.5- to 11-fold greater than that of an unaffected male. The higher the testicle is located, the higher the risk (Kinkade, 1999). Infantile hernia is also an established risk factor (Ryder et al, 1997).

Hormonal. A prenatal etiology has been suggested for testicular germ cell cancer. The main hypothesis is that high concentrations of unbound maternal estrogens in utero are the exposure of importance (Swerdlow et al, 1997). Some data suggest that women carrying fraternal twins have even higher amounts which may account for higher incidence among twins (Swerdlow et al, 1997). The low incidence among African American men may also relate to prenatal hormonal exposure. Henderson et al (1988) postulated that increased testosterone levels in black women during early pregnancy compared with white women may provide a protective effect in male offspring. Two recently published Canadian studies confirmed an increase in testicular cancer from 1964 to 1996 (60%) and established an association with pre-term birth, first birth among mothers below the age of 24 at conception, treatment for undescended testicle and exogenous hormone exposure (Weir et al, 1999; Weir et al, 2000). Pre-term birth and first birth to young mothers is associated with elevated levels of maternal hormone exposure (Weir et al, 2000). There has also been a suggestion that sons whose mothers were exposed to a hormone diethylstilbestrol (DES) may be at higher risk, although this has not been confirmed (http://cancer.gov/cancerinformation). Furthermore, a hormone has recently been implicated in the regulation of testicular descent in mice (Nef & Parada, 1999).

Environmental. Considerable attention has been paid to the potential role of "environmental hormones," chemicals in the environment that may alter or mimic the activity of feminizing hormones. Declines in fertility of many animal species have been linked to pollutants' disruption of endocrine function. Data tying similar reproductive abnormalities in humans to endocrine disruptors is not conclusive. Evidence against such a link with testicular cancer and other hormonally sensitive cancers include large differences in incidence and mortality in terms of geography and ethnic groups, and rising rates that preceded widespread use of PCBs and DDT. For example, incidence rates are high in Denmark but low in Finland, countries that are similar in patterns of economic development, diet and use of chemicals (Safe, 2000). "In short, the epidemiological data on cancers of hormonally sensitive tissues and the data on sperm count in men do not provide consistent or convincing evidence of an effect associated with exposure to those chemicals accused of being endocrine disrupters" (American Council on Science and Health, 1999).

Occupational. Several occupations have been associated with an increased risk of testicular cancer. Mixed results have been found for farmers and allied workers, with suggestions that pesticides and sex hormones may be causal agents (Ryder et al, 1997; Knight et al, 1996). Dimethylformamide has been implicated in elevated incidence of testicular cancer among leather tanning and aircraft workers, leading OSHA to issue a hazard bulletin in 1988 (Levin et al, 1987; Ducatman et al, 1986; http://www.osha-slc.gov/dts/hib/hib_data/hib19880217.html). Higher incidence of nonseminoma-type testicular cancer has also been reported among miners - including oil and gas workers (Knight et al, 1996), and food and beverage processing workers, especially meat and bakery workers (Knight et al, 1996). Risk was also elevated for janitors, kitchen workers, and utility company employees, especially in the electrical power industry. Some of the groups at risk - particularly the food and beverage processors, janitors, and kitchen workers - shared some common characteristics, such as on-the-job use of cleaning agents, disinfectants, and insecticides (Knight et al, 1996). Seminoma-type cancers tend to be more

frequent among better-educated men, who are less likely to be exposed to potentially toxic substances on the job. This raises the possibility that toxic exposures at work could cause seminoma-type testicular cancers to convert to the faster-developing nonseminoma type (Knight et al, 1996). Parental occupation may also play a role (Ryder et al, 1997).

B. Need for This Study

The public health significance of the proposed study is to clarify potential relationships between genetic and environmental factors. A case-control study among a military population provides an ideal opportunity to examine the etiology of this disease in a high-risk group. Data available from the DoD Serum Repository, Tumor Registry, and Medical Surveillance System, coupled with additional data collected through interviews and laboratory tests, will permit a more complex study of the many factors that together might shed light on this cancer that affects otherwise healthy young men.

C. Subject Selection Procedures and Eligibility Criteria

The STEED project will attempt to contact 1,200 case subjects. Approximately 1,080 cases among active duty and non-active duty servicemen with testicular cancer and 1,080 matched controls among servicemen without testicular cancer will be enrolled by Battelle in the study. The mothers of each enrolled case and control will also be asked to participate. All cases and controls will be identified from among those who contributed blood samples to the DoD Serum Repository (DoDSR) between the years 1989 and 2002.

Eligibility criteria for cases include:

1. Existence of a serum sample in the DoDSR before diagnosis
2. Age between 18 and 45 at time of diagnosis
3. Confirmed diagnosis of testicular germ cell cancer, and
4. On active duty at time of diagnosis

Eligibility (matching) criteria for controls include:

1. DOB (+/- 1 year of Cases),
2. Ethnicity, (European-American/white, African-American/black, other),
3. Date of serum donation (+/- 30 days of the case donation date),
4. Never had a diagnosis of testicular germ cell cancer (other cancer is OK),
5. Must have been on active duty at time of diagnosis, and
6. Existence of a serum sample in the DoDSR